v. 4, n. 2, 2024

International Journal of Health Science

ANOREXYGENOUS MEDICINES FOR CONTROLLING OBESITY IN CHILDHOOD AND ADOLESCENCE

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Abstract: Childhood obesity is increasingly prevalent and can be associated with significant short- and long-term health consequences. In some serious cases of obesity, when changing lifestyle habits and diet are not enough to reduce weight, anorectic medications can be used. This work aims to describe, through a literature review, the main drugs used for weight loss in children and adolescents, their mechanism of action and effectiveness. Emphasizing medicines with greater literary support. A search was carried out in the PUBMED and Google Scholar databases. Used the following descriptors: *Anorexigenic drugs, Pediatric Obesity, weight loss.* Articles were selected between 2004 and 2022. For the selection of articles, preference was given to systematic reviews and in vivo studies. In pediatric patients with severe obesity, anorectic medications can be used along with changes in lifestyle and diet to reduce weight. Despite this, data on long-term efficacy and safety and undesirable side effects present a challenge for using medications to treat pediatric obesity.
Keywords: Anorectic drugs, Pediatric obesity, Weight loss.

INTRODUCTION

Obesity was considered one of the five diseases that pose the greatest health risks in 2015, by the World Health Organization (CHEN, 2016). In the world, there are around two billion overweight and obese people, and Brazil occupies fifth place in the world ranking, with around 18 million people, reaching up to 70 million overweight individuals (GARCIA RAMIREZ et al, 2020). In this context, the prevalence of childhood obesity has increased considerably in the last four decades, with 50 million girls and 74 million boys considered obese worldwide, aged between 5 and 19 years (NALLY et al, 2021).

Due to the increase in the number of

obese children around the world, especially in underdeveloped countries, childhood obesity has been reported as an epidemic. The childhood obesity epidemic has become a serious public health problem worldwide and is a major public health challenge of the 21st century (MEAD et al, 2016). Furthermore, there is great concern as obesity has serious social and health consequences in adult life, such as its related comorbidities (HILL et al, 2011).

Overweight or obese children are more likely to develop other chronic diseases such as type 2 diabetes, non-alcoholic fatty liver disease, polycystic ovary syndrome, asthma, obstructive sleep apnea, pseudotumor cerebri, gastroesophageal reflux disease and orthopedic problems. An association between childhood obesity and coronary artery disease in adulthood also exists. Obese children are also more likely to have precocious puberty (KENDRICK et al, 2015). In addition to chronic diseases, obese children and adolescents are susceptible to psychological problems due to low self-esteem and self-concept, reduced quality of life, depression and/or social discrimination (HILL et al, 2011).

When these comorbidities are associated with severe childhood obesity, therapeutic intervention with medication can be used to a limited extent in the pediatric population. In Brazil, the medications liraglutide, orlistat and sibutramine are approved for use as anorectics. However, drugs approved for other indications have been used to promote weight loss (off-label use). These drugs include anticonvulsants, drugs used to control diabetes and antidepressants. Despite this, in Brazil there are no anti-obesity drugs approved for pediatric use.

METHODOLOGY

The search for articles in this bibliographic review was carried out in the PUBMED and Google academic databases. Used the following descriptors: *Anorexigenic drugs, Pediatric Obesity, weight loss*. Articles were selected between 2004 and 2022. For the selection of articles, preference was given to systematic reviews and *in vivo* studies.

DISCUSSION

DEFINITION OF CHILDHOOD OBESITY

Obesity is a chronic condition characterized by excess body fat. It is often defined by the body mass index (BMI), which directly relates to body fat. BMI is given as the ratio of weight in kilograms to height in meters squared (kg/m2). In children and adolescents, BMI varies with age and gender. Thus, a given BMI value is usually compared with reference charts to obtain a BMI percentile ranking for age and gender. The BMI percentile indicates the relative position of the child's BMI compared to a historical reference population of children of the same age and gender (CANOY & BUNDRED, 2011). When an individual is between 2 and 18 years old, with a BMI above the 85th percentile and below the 95th percentile, he or she is overweight. Percentiles above 95 indicate obesity and the need for intervention (WALD & ULI, 2009).

ANORECTIC MEDICATIONS

LIRAGLUTIDE

Liraglutide is a peptide-1 receptor agonist (GLP-1 analogue) that works by stimulating the release of insulin, delaying gastric emptying, and regulating the release of postprandial glucagon. As a result, there is a reduction in food intake. Liraglutide is used for the treatment of type 2 diabetes mellitus, but in 2014 it was approved for the treatment of obesity (BERSOUX et al, 2017).

This medication can be used in individuals over 12 years of age, as an adjunct to lifestyle

changes. A dose of 3mg/per day has been shown to be effective in reducing BMI. The adverse effects reported in a study with patients in this age group were most often mild and moderate, with gastrointestinal changes being the most common (KELLY et al, 2020).

ORLISTATE

Orlistat is a pancreatic and gastric lipase inhibitor medication, meaning that the fat ingested is not completely hydrolyzed. For this reason, this appears to be a good drug of choice for weight loss drug therapy due to its safe cardiovascular risk profile and beneficial effects on lipid levels (BERSOUX et al, 2017).

The dose used in patients over 12 years of age is 120 mg three times a day and must be associated with a low-fat diet. Most adverse effects of the medication orlistat are related to the gastrointestinal tract, with most reports being mild to moderate in intensity. These adverse events include steatorrhea, fecal urgency, flatulence with oily patches, abdominal pain and possible contribution to vitamin D deficiency (CHANOINE et al., 2005). Despite this, orlistat has a good safety profile, as systemic absorption is minimal. Multivitamin supplementation is strongly recommended. Monitoring the level of 25-hydroxyvitamin D may be considered (DOLINSKY et al, 2013).

In a randomized controlled clinical study with 539 adolescent patients from different regions, it was demonstrated that orlistat reduces BMI by 5% when compared to control. Medication must be indicated in association with exercise, lifestyle changes and diet (CHANOINE et al., 2005).

SIBUTRAMINE

Sibutramine is a neurotransmitter reuptake inhibitor that reduces the reuptake of serotonin, norepinephrine and dopamine and increases satiety. Furthermore, it also has the ability to stimulate thermogenesis (POSTON & FOREYT, 2004). The success of sibutramine as a weight loss agent in adults justified its investigation in adolescents. Sibutramine was initially approved for weight loss in adults in 1997 and is currently FDA approved for ages 16 and older, although safety concerns have limited its use in the pediatric population (DOLINSKY et al, 2013).

Several short-term double-blind placebo-controlled randomized clinical trials in adolescents have documented the efficacy of sibutramine in reducing weight and BMI when combined with low-calorie diet and exercise or with behavioral therapy (GODOY-MATOS et al, 2017; GARCIA-MORALES).

The recommended dose for this drug is between 10 and 15 mg daily. When the patient does not tolerate high doses very well, a daily dose of 5 mg can be administered. Significant safety concerns with the use of sibutramine in the pediatric population concern the cardiovascular system and include increases in blood pressure and pulse rate. Other side effects caused by sibutramine include dizziness, dry mouth, constipation and insomnia. Therefore, heart rate and blood pressure must be monitored (DOLINSKY et al, 2013).

Sibutramine must not be administered to patients with poorly controlled hypertension or cardiovascular disease. Additionally, there are reports of manic episodes, psychotic episodes, and panic attacks attributed to the use of sibutramine. Therefore, it is contraindicated in adolescents with pre-existing psychiatric disorders (DOLINSKY et al, 2013).

FLUOXETINE

Fluoxetine has been used as an off-label medication for weight management. It acts as a serotonin reuptake inhibitor and is indicated

in the treatment of depression. Serotonin is a neurotransmitter that reduces food intake by preventing the transport of serotonin from the extracellular space to the serotonin nerve terminals. The higher extracellular concentration of serotonin has the functional consequence of decreasing food intake. This occurs through changes in appetite, resulting in decreased food intake and normalization of unusual eating behaviors (SERRALDE-ZÚÑIGA et al, 2019).

Fluoxetine can be used in patients from 6 years of age. The dose of fluoxetine can vary from 10 to 20 mg per day. Some side effects observed when using fluoxetine are dry mouth and loose stools (REZVANIAN et al, 2010).

METFORMIN

Although metformin's label specifies diabetes as the sole indication, the drug has been prescribed with increasing frequency to overweight and obese patients with impaired fasting blood glucose after metformin administered over long periods was shown to prevent diabetes and induce weight loss. weight (YEREVANIAN et al, 2019). Metformin is known to induce modest weight loss in overweight patients, even without glucose abnormalities, and is prescribed off-label as an adjunct to weight loss.

Metformin can be used at 250-1000 mg twice a day. Studies with children and adolescents still have a short evaluation period and therefore more studies must be carried out. Despite this, the adverse effects of metformin are mild and transient, such as flatulence, bloating, nausea and diarrhea. Metformin must not be used in patients with renal failure and must be discontinued in any patient who develops severe illness, decreased perfusion or when undergoing intravenous contrast exams (WALD & ULI, 2009).

PHENTERMINE

Fetermine is a medication approved in the United States for adolescents over the age of 16 for use for a period of up to 12 weeks. The mechanism of action of this drug is based on reducing the reuptake of norepinephrine, serotonin and dopamine, improving inhibitory control of appetite (SINGHAL et al, 2021). The usual prescribed dose is 15 mg, 30 mg or 37.5 mg per day. The most common side effects are irritability, insomnia, mood changes, dry mouth, dizziness, tremor, headache, elevated heart rate and blood pressure and gastrointestinal side effects (WOODARD et al, 2020). Contraindications include a history of past or uncontrolled cardiovascular disease, hyperthyroidism, glaucoma and current use of monoamine oxidase inhibitors (SINGHAL et al, 2021).

TOPIRAMATE

Topiramate was approved by the FDA for the treatment of refractory epilepsy in 1996. Weight loss was immediately noted as a side effect. Soon after this, reports began to appear that topiramate was effective in treating binge eating disorder. It is not approved as a monotherapy for obesity. However, patients using it to treat seizures or psychiatric disorders (e.g., binge eating, borderline personality disorder) have reported weight loss during treatment. The mechanism of how the drug promotes weight loss is not yet well described, but includes inhibition of taste by carbonic anhydrase, influences on the transmission of gamma-aminobutyric acid - causing appetite suppression, sensitization of insulin activity and secretion of adiponectin in tissues peripherals (BERSOUX et al, 2017). However, in pediatrics, when prescribing for obesity, side effects such as drowsiness, lethargy, attention disorder, fatigue and irritability must be considered, which can compromise learning (SINGHAL et al, 2021).

EFFICACY OF ANORECTIC MEDICATIONS FOR CONTROLLING CHILDHOOD OBESITY

The medicinal efficacy of anorectic medications related to childhood obesity was evaluated through a systematic review. Where 21 randomized clinical studies were selected. With a total of 2,484 participants from the included studies, 1478 participants were randomized to drug intervention and 904 to comparison groups. The duration of the intervention period varied from 12 weeks to 48 weeks, and follow-up occurred from the beginning of treatment until six months to 100 weeks. When divided by type of drug, sibutramine, metformin and orlistat treatments demonstrated reductions in BMI in favor of the intervention. BMI was also reduced for all medications evaluated. Despite this, adverse events were reported and the most common in studies with orlistat and metformin were gastrointestinal (such as diarrhea, mild abdominal pain or discomfort, fatty stools). The most frequent adverse events in sibutramine studies included tachycardia, constipation, and hypertension. The only trial with fluoxetine reported dry mouth and loose stools. Thus, the review demonstrated that pharmacological interventions (metformin, sibutramine, orlistat and fluoxetine) in obese children and adolescents may have small effects in reducing BMI and body weight in obese children and adolescents. However, many of these medications are not licensed for the treatment of obesity in children and adolescents (MEAD et al, 2016).

On the other hand, another systematic review highlighted the importance of healthy lifestyle habits in children and adolescents as the main method of prevention and treatment and highlighted that scientific evidence did not support the use of anorectic medications in patients under 12 years of age. After this age, the use of orlistat or sibutramine may be considered as a complement to lifestyle interventions, although this approach needs to be carefully evaluated for potential adverse effects).

Lifestyle modification is emphasized as the basis for any additional pharmacological therapy. If pharmacological therapy is necessary, even *off-label*, use must be carefully evaluated and discontinued in case of lack of efficacy. When pharmacotherapy is considered, only clinicians experienced in the use of the agents must use them (STYNE et al, 2017).

FINAL CONSIDERATIONS

In pediatric patients with severe obesity, anorectic medications can be used along with changes in lifestyle and diet to reduce weight. Despite this, data on long-term efficacy and safety and undesirable side effects present a challenge for using medications to treat pediatric obesity.

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